REMARKS

A. Regarding the Amendments

Upon the entry of the amendment, claims 1-10, and 15-22, will be pending. Claims 1-4, 7, 10, 15-17, and 19 have been amended to claim the subject matter of the invention with greater particularity and specificity. The specification has been also amended to provide a generic meaning to the trade name Trasylol®. Amendments to claims and specification merely clarify the language of claims and specification. No new matter has been introduced by the amendments.

Claim 1 now recites "human Kunitz-type serine protease inhibitor." The limitation "human" is disclosed throughout the original specification. See, e.g., page 10, line 33.

Newly added claim 22 now includes the limitation

> "wherein the rate of mucociliary clearance is increased by more than about 30 per cent, compared with the rate of mucociliary clearance in the absence of the treatment."

This limitation is supported by the specification, for instance, by Example 21 (page 80, line 35 through page 81, line 4), as further illustrated by FIG. 22. As can be seen from the chart on FIG. 22, 8 hours after administering 3 ml of 3 mg/mL aerosol of the inhibitor bikunin, the tracheal mucus velocity (TMV) for a sheep was at about 98 % of the baseline, while for the vehicle only, the TMV was about 76 %. Accordingly, using the inhibitor increased the TMV by about 30%. In Example 25, as illustrated by FIG. 26, a substantial increase in the value of the TMV was also observed. As shown by FIG. 26, 2.5 hours after administering the inhibitor, the increase in the value of the TMV was more than 30 %, i.e., from about 3 mm/min average for compositions with HBSS only (no inhibitor), to about 9 mm/min average, the increase being about 200% over HBSS treatment.

Additionally, the Examiner requested the Applicants to re-submit a copy of the sequence listing in a computer readable form (CRF) (paragraph [9] on page 3 of the Office Action). A computer disk having the sequence, and a declaration stating compliance with 37 C.F.R. § 1.821 (f) are attached herewith.

The Substituted Sequence Listing submitted herewith is indential to the previously filed Listing with the exception of the new docket number.

B. Objections to the Specification

In paragraph [10] on page 4 of the Office Action the Examiner objected to the use of trademark Trasylol® because it is not capitalized throughout the specification. The Examiner also required to provide the generic meaning of the trademark. The Applicants respectfully point out that using of the trademark symbol ® following the word is a permissible alternative to capitalization (see, MPEP § 608.01(v), right-hand column on page 600-88 of the MPEP). The Applicants added a generic description of the trade name. Accordingly, the withdrawal of the objection is respectfully requested.

C. Rejection Under 35 USC § 112, First and Second Paragraphs and Double Patenting Rejection

The Applicants have noted and acknowledged the fact that the Examiner has withdrawn the previous rejections under 35 USC § 112, first and second Paragraphs (paragraphs [11]-[13] on pages 4-5 of the Office Action). The Applicants have also noted and acknowledged the fact that the Examiner has withdrawn the previous double patenting rejection (paragraph [16], page 6 of the Office Action).

D. Rejection Under 35 U.S.C. § 103 (a)

Claims 1-10, 15-17, and 19 have been rejected under 35 U.S.C. § 103(a) as allegedly being obvious over the patent document WO 97/33996 (Tamburini et al.) in view of the article by Rasche et al. and the article by O'Riordan et al. (paragraph [14] page 5 of the Office Action). This rejection is respectfully traversed on the following grounds.

To establish a *prima facie* case of obviousness, the following three basic criteria must be met: (1) there must be some suggestion or motivation to modify the reference(s) as proposed by the Examiner; (2) there must be a reasonable expectation of success and (3) the prior art reference(s) must teach or suggest all of the claim limitations. The Applicant respectfully submits that none of the criteria have been satisfied in this case because Tamburini et al. do not disclose or suggest every limitation of claims 1-10, 15-17, and 19, and the combination of Rasche et al. and O'Riordan et al. fails to cure this deficiency.

In order to be a proper prior art reference, Tamburini et al. must disclose the method treatment of a patient using the Kunitz-type serine protease inhibitor having at least one sequence specified in claim 1. As a result of such treatment, the rate of mucociliary clearance must increase. None of these limitations is disclosed by Tamburini et al. All that is described by Tamburini et al. is the use of a Kunitz family serine protease inhibitor such as a placental bikunin (page 2, lines 32-34). There is no teaching anywhere in Tamburini et al. which discloses that as a result of treatment, the rate of mucociliary clearance is increased as recited in claim 1. The Examiner has clearly recognized the lack of disclosure regarding the rate of mucociliary clearance (see, page 13, lines 5-6 of the previous Office Action dated 10/01/03, to which Office Action the Examiner referred in the instant Office Action). Additionally, there is no disclosure in Tamburini et al. showing that the rate of mucociliary clearance is increased by "more than about 30 per cent" as recited in claim 22.

Short of the direct teaching, alternatively, there must be a suggestion or motivation in Tamburini et al., or in Rasche et al., or in O'Riordan et al., or in any combination of these references, to modify what is described in Tamburini et al. to arrive at the subject matter of claim 1. It is submitted that there is no such suggestion or motivation. Contrariwise, the disclosure of Tamburini et al. is incompatible with the disclosure of Rasche et al., and in addition there is no indication whatsoever that the disclosures of Rasche et al. and of O'Riordan et al. can be combined.

Indeed, Tamburini et al. teach only the use of a human protein, i.e., human placental bikunin (page 2, lines 29-34). Tamburini et al. teach that there are "problems" with aprotinin, which is of "bovine origin" (page 2, lines 8-9). Specifically, Tamburini et al. disclose that using aprotinin involves a "risk of anaphylaxis" (page 2, lines 9-10) and the risk of kidney damage because aprotinin is "nephrotoxic in rodents and dogs" (page 2, line 13). There is no question that the entire purpose of the Tamburini et al. reference is to provide a human replacement to aprotinin. It can be, therefore, safely concluded that Tamburini et al. **teach away** from using aprotinin.

To contrast, Rasche et al. discuss exclusively the use of aprotinin to treat chronic obstructive bronchitis. Rasche et al. disclose no other protein. Since Tamburini et al. advise against using aprotinin, there is a strong indication that one having ordinary skill in the art would not be motivated to use the protein disclosed in Tamburini et al. to treat bronchitis using the procedure disclosed by Rasche et al. In addition, all that is disclosed by Rasche et al. is achieving less airway resistance ("impressive airway resistance drop") as well as making the "initially very viscous sputum" liquid-like (Section 4, fourth full paragraph of the English translation). There is nothing disclosed with regard to the rate of mucociliary clearance. To conclude that the rate of mucociliary clearance will increase just because the airway resistance and the viscosity of the sputum dropped would be speculative. It is possible to have a situation when the airway resistance has dropped and the sputum has liquefied and yet the mucociliary

clearance has not improved for reasons other that the airways resistance or the viscosity of the sputum.

Turning now to the O'Riordan et al. reference, it is disclosed the treatment of mucociliary dysfunction may be caused by antigens. The point of Rasche et al. and O'Riordan et al. references is that serine protease inhibitors , like aprotinin, would block elestatse, which might improve lung function in bronchitis or asthma. However, it is known in the art that elastase is not involved in mucociliary clearance. Neither Rasche et al. nor O'Riordan et al. disclosed that specific serine proteases, e.g., channel activating proteins, such as prostasin, are inhibited which directly effects mucociliary clearance.

Accordingly, the combination of the disclosures of Rasche et al. and O'Riordan et al. fails to describe every element of claim 1. In addition, even if two disclosures are combined, the O'Riordan et al. reference does not improve the case for obviousness because no specific proteins are disclosed by O'Riordan et al.

In view of the foregoing, it is respectfully submitted that claim 1 is distinguishable over the references cited by the Examiner. Claims 2-10, 15-17, and 19 depend, directly or indirectly, on claim 1, and are allowable for at least the same reason. Reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, reconsideration and favorable action on all claims are respectfully requested. In the event any matters remain to be resolved, the Examiner is requested to contact the undersigned at the telephone number given below so that a prompt disposition of this application can be achieved.

A check in the amount of $110.00 is enclosed to cover the One Month Extension of Time fee. If any additional fee is required, the Commissioner is hereby authorized to charge any other fees associated with the filing submitted herewith, or credit any overpayments to Deposit Account No. 07 -1896.

Respectfully submitted,

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